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PHOTOCHEMICAL DIMERIZATION OF β-CARBOLINE ALKALOIDS

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Abstract—Irradiation of β-carboline derivatives gives two products involving the formation of new N-N or N-C bonds.

On the basis of MS and ^{1}H-NMR data dimeric structures were established. Some aspects of the photophysical process and of the radical nature of these dimerization reactions are discussed.

Despite the growing interest in the photochemistry of alkaloids[1] the effect of UV light on β-carboline derivatives has not been studied. McKenna *et al.*[2] studied the UV mediated cytotoxic activity of β-carboline alkaloids using yeast and bacterial bioassay systems. Now we want to report our findings on UV irradiation of these compounds.

When a solution of harmane (1-methyl-9H-pyrido(3, 4-b)indole) in dichloromethane was irradiated with a high pressure Hg lamp, two products with very different Rf values were obtained. The possibility that these products were formed through a dark reaction was discarded studying the thermal stability of harmane in the same solvent at 60–70° for 15 h.

The reaction mixture was chromatographed on a neutral aluminum oxide column and besides the non-converted harmane (Rf 0.70) two colorless substances were eluted: compounds **2** (Rf 0.85) and **3** (Rf 0.46) in yields of 8 and 48% respectively (Table 1).

The UV spectra of **2** and **3** were almost identical to that of harmane (Table 1). This result suggests that the β-carboline ring was not modified excluding the formation of rearranged products. It is known[3] that by UV irradiation of pyridine valence isomers could be formed: azaprismane, azabenzvalene and Dewar pyridine and these intermediaries are transformed into more stable products:[4] α-, γ- and δ-carbolines.[5]

In the IR spectrum of **3** the NH signal appears at 3450 cm^{-1}. It is interesting to mention that the same signal was absent in the IR spectrum of **2**. This fact was confirmed by the ^{1}H-NMR spectra of the same products.

The MS of **2** and **3** showed important peaks at *m/z* 362. This value agrees with the molecular ion of a β-carboline dimer. Also in the ^{1}H-NMR spectra of **2** and **3** the value of the ratio between the area of aromatic protons together with that of the NH group, and the area of the Me groups (6:3) was different from that of harmane (7:3), indicating that these compounds were formed by dehydrogenation of two harmane molecules and dimerization.

It is noteworthy that the MS of **2** shows the base peak at *m/z* 181 (M/2) and there are not peaks between M and M/2 (MS data are given in Experimental Section). This result would indicate that the dimer **2** has a symmetric structure. On the other hand, in the MS of **3** some signals appear at *m/z* values between M and M/2; it could be explained as coming from an asymmetric dimer. These suppositions were confirmed by ^{1}H-NMR spectroscopy because in the spectrum of **2** only one signal appears for the Me groups whereas in that of **3** the two Me groups absorb at different δ values.

The same photoreaction was then applied to harmine (7-methoxy-1-methyl-9H-pyrido(3, 4-b)indole), giving the corresponding dimeric products **4** and **5** whose MS showed a molecular ion (*m/z* 422) related to that of **2** and **3**. On the other hand, the irradiation of nor-harmane (9H-pyrido(3, 4-b)indole) afforded only one dimer (**1**) with properties similar to those of **2** and **4**.

When 1-ethyl-β-carboline (1-ethyl-9H-pyrido(3, 4-b)indole) was irradiated poor results were obtained. In spite of the high conversion (80%) the photodimers were isolated in very low yields (< 3%). Their structures were correlated with those of the above mentioned dimers by comparing the Rf (**6** 0.77 and **7** 0.42) and MS data.

A different result was obtained when a dihydro-β-carboline (3, 4-dihydro-harmine) was irradiated. The photolysis in acidic medium (Cl_2CH_2-HCl or EtOH-HCl) yielded only the fully aromatic alkaloid (harmine); when the same substrate was irradiated in Cl_2CH_2 the non-converted alkaloid (85%), together with unidentified polymers, was recovered.

According to the TLC behavior the products could be classified into two series. The symmetric character and the absence of NH groups agree with the higher Rf value of **1**, **2**, **4** and **6** compared with those of the asymmetric products, **3**, **5** and **7**.

The yields, the physical and spectroscopic properties of the compounds obtained are indicated in Table 1 and in the Experimental section.

It is known that by UV irradiation pyridine yields 1, 2- and 1, 4-diradicals.[6,7] The dimerization of these radicals in symmetric (head to head) or in asymmetric form (head to tail), through intermediates such as cyclobutane or cyclo-octane could form a great variety of products.

Taking into account: (i) the *m/z* value of the molecular ion (MS); (ii) the number of aromatic and NH protons (^{1}H-NMR); (iii) the UV absorption spectra and (iv) the MS and ^{1}H-NMR spectra, we were able to discard the structures that were not formed through an oxidative photodimerization ((i) and (ii)) and then the remaining structures because they did not fulfil conditions (iii) and (iv).

On the other hand, if the photoreactivity is located at the NH group, two dimers (**A** and **B**, Scheme 1) could be formed whose structures agree with conditions i-iv.

Table 1. Physical and spectroscopical properties of the β-carbolines and their dimeric photoproducts

compound	yield^a (%)	m.p. (°C)	Rf^b	U.V λmax(nm) (logε); EtOH	^{1}H-NMR δ(ppm); DMSO-d_6 / TMS$_{int}$		
					aromatic protons	CH_3	NH^c
nor-Harmane		198-200**	0.75	234 (4.90); 250 sh(4.86) 282 (4.52); 289 (4.60) 339 (4.20); 352 (4.24)	H_1 9.00 (s) H_3 8.43 (d, $J_{3,4}$ 5 Hz) H_5 8.26 (d, $J_{5,6}$ 8 Hz) H_4 8.13 (d, $J_{3,4}$ 5 Hz) H_7 and H_8 7.65 (m); H_6 7.30 (m)		11.66 (s)
I^d	26	223-224	0.87	227 (4.95); 279 sh(4.46) 282 (4.58); 331 (4.12) 339 (4.15)	H_3 8.58 (d, $J_{3,4}$ 5.5 Hz) H_5 8.48 (d, $J_{5,6}$ 8 Hz) H_1 8.40 (s) H_4 8.36 (d, $J_{3,4}$ 5.5 Hz) H_6 and H_7 7.60 (m); H_8 6.94 (m)		
Harmane		238 239*	0.70	234 (4.89); 238 (4.90) 249 sh(4.75); 281 (4.20) 288 (4.25); 335 (3.67) 348 (3.69)***	H_3 8.27 (d, $J_{3,4}$ 5 Hz) H_5 8.22 (d, $J_{5,6}$ 8 Hz) H_4 7.93 (d, $J_{3,4}$ 5 Hz) H_7 and H_8 7.65 (m); H_6 7.28 (m)	2.85 (s)	11.60 (s)
II^c	8	185-188	0.85	230 (4.86); 278 sh(4.28) 281 (4.40); 327 (4.05) 339 (4.11)	H_3 8.68 (d, $J_{3,4}$ 5.5 Hz) H_5 8.62 (d, $J_{5,6}$ 8 Hz) H_4 8.43 (d, $J_{3,4}$ 5.5 Hz) H_6 and H_7 7.80-7.50 (m); H_8 6.99 (m)	1.92 (s)	
III^d	48	300-301	0.46	236 (5.00); 251 sh(4.51) 286 sh(4.19); 338 (3.84) 350 (3.91)	H_4 8.34 (s); $H_{3'}$, H_5 and $H_{5'}$ 8.33 (m) $H_{4'}$ 8.10 (d, $J_{3',4'}$ 5.5 Hz) H_7 and H_8 7.75-7.50 (m); H_6 7.41 (m) $H_{6'}$ 7.30 (m) $H_{7'}$ and $H_{8'}$ 7.23-7.09 (m)	2.85 (CH_3, s) 2.13 (CH_3', s)	11.89 (s)

Harmine[f]		260-261*	0.62	241 (4.96); 261 sh(4.86)	H_3 8.16 (d, $J_{3,4}$ 5 Hz)	2.75 (s)	11.35 (s)
				301 (4.66); 325 (4.20)	H_5 8.03 (d, $J_{5,6}$ 8 Hz)	3.88 (OCH_3, s)	
				338 (4.32)	H_4 7.77 (d, $J_{3,4}$ 5 Hz)		
					H_8 7.03 (d, $J_{6,8}$ 2 Hz)		
					H_6 6.85 (dd, $J_{5,6}$ 8 Hz; $J_{6,8}$ 2 Hz)		
V[d]	75	298-300	0.43	247 (4.98); 304 (4.61)	$H_{3'}$ 8.28 (d, $J_{3',4'}$ 5.5 Hz)	2.81 (CH_3, s)	11.74 (s)
				328 sh(4.23); 334 (4.23)	$H_{5'}$ 8.20 (d, $J_{5',6'}$ 8 Hz)	2.06 (CH_3', s)	
					H_4 8.17 (s)	3.90 (OCH_3, s)	
					H_5 8.16 (d, $J_{5,6}$ 8 Hz)	3.71 (OCH_3', s)	
					$H_{4'}$ 7.96 (d, $J_{3',4'}$ 5.5 Hz)		
					H_8 7.13 (d, $J_{6,8}$ 2 Hz)		
					$H_{6'}$ 7.00 (dd, $J_{5',6'}$ 8 Hz; $J_{6',8'}$ 2 Hz)		
					H_6 6.86 (dd, $J_{5,6}$ 8 Hz; $J_{6,8}$ 2 Hz)		
					$H_{8'}$ 6.65 (d, $J_{6',8'}$ 2 Hz)		

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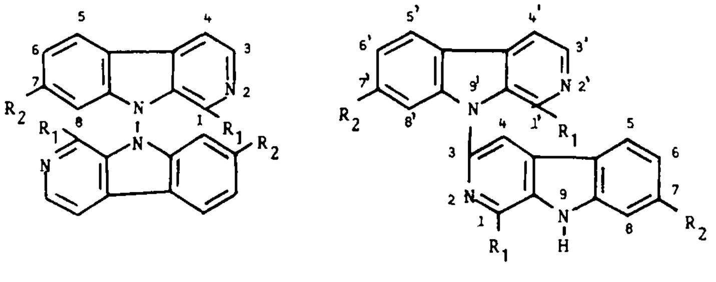
a) conversion %: nor-Harmane 82; Harmane 54 and Harmine 56. Yields were calculated from converted substrate.
b) tlc: neutral aluminum oxide; benzene-EtOH.
c) in all examples this signal disappeared by adding D_2O.
d) molecular formulae was determined from MS and microanalysis data.
e) molecular formulae was determined from MS data.
f) the dimer IV was obtained in low yield (<3%); it has a Rf 0.72 and its MS is given in Experimental.
* Ref. 34
** Ref. 35
*** UV data of Harmane in different solvents: (EtOH-HCl) 236(4.73), 239(4.93), 253sh(4.60), 280(4.35), 300(4.28), 360(3.68); (Cl_2CH_2) 236(4.85), 238(4.92), 250sh(4.70), 285(4.21), 290(4.28), 328(3.67), 342(3.68); (Cl_2CH_2-HCl) 235(4.76), 238(4.90), 280(4.35), 298(4.12), 332(3.62), 360(3.54).



1 $R_1 = R_2 = H$
2 $R_1 = Me$ $R_2 = H$
4 $R_1 = Me$ $R_2 = OMe$
6 $R_1 = Et$ $R_2 = H$

3 $R_1 = Me$ $R_2 = H$
5 $R_1 = Me$ $R_2 = OMe$
7 $R_1 = Et$ $R_2 = H$

Scheme 1.

In Scheme 1 we do not include structures with $N_{9'}$-C_4 bond and those in which the $N_{9'}$ and the different positions of the benzene ring are joined because they are in disagreement with ^{1}H-NMR and MS data.

By comparing the ^{1}H-NMR spectra of **2** and harmane (Table 1) we can observe a shielding effect on H_8 and CH_3 groups which together with the absence of NH group suggests a structure like **A** for dimer **2** (Scheme 1). The two harmanyl moieties are bonded through the indolic N atoms and lie in almost perpendicular planes thus the unshared N electrons are *gauche* to each other giving a stable conformation.[8]

A similar analysis could be made of the ^{1}H-NMR spectrum of dimer **1**, in which the H_1 and H_8 are the only aromatic protons shifted to higher fields.

In the MS of **1** and **2** we observed that the principal decomposition is the homolysis of the N–N bond giving the cation M/2 as the base peak. All the other signals originate from this cation and are typical of β-carboline alkaloids.[9]

A similar fragmentation pattern can be recognized in the MS of **4** and **6**.

The ^{1}H-NMR spectrum of **5** is a good example of an asymmetric structure. All the signals may be assigned, and they suggest a structure such as **B** (Scheme 1) for the dimer in which two harmanyl groups are joined by a $N_{9'}$–C_3 bond. As in the case of the symmetric dimers, the Me' group and the $H_{8'}$ are the most shifted signals with respect to those of harmine.

The ^{1}H-NMR spectrum of **3** also agrees with a **B** structure.

The asymmetric character proposed for **3** and **5** was confirmed by MS data. As an example, the MS of **3** shows the molecular ion as the base peak and the M–H peak with an abundance of 98%.

Also, starting from $M^{+\cdot}$ the typical fragmentation of β-carboline alkaloids[9] involving the pyridine ring is observed: $M^{+\cdot}$-Me (or $M^{+\cdot}$-H-Me) *m/z* 347 (17%) and $M^{+\cdot}$-MeCN (or $M^{+\cdot}$-H-MeCN) *m/z* 321 (5%). Among the fragmentations originated in $M^{+\cdot}$, the HCN loss (*m/z* 335, 8%) is characteristic of a pyridine ring without substituent at C_3, whereas the RCN (R = Harmanyl group) (*m/z* 155–153) and RCNCMe loss (*m/z* 128–126) are typical of a β-carboline substituted at C_3. These fragmentations are responsible for the different abundance observed for the peaks smaller than M/2 with respect to that of harmane.[9]

Taking into account the known[10–12] benzidine photorearrangement of compounds like $(RPhN(Me)\text{-})_2$ and $(Ph_2N\text{-})_2$ we attempted to determine whether **A** is the precursor of **B** by studying their thermal (in Cl_2CH_2 soln at 60–70° for 15 h) and photochemical behavior. The independent formation of these photodimers was demonstrated because no interconversion was observed during experiments carried out with **A** or **B**.

Also, we submitted the symmetric dimers to the usual conditions of the hydrazobenzene–benzidine rearrangement[10–13] at 70° and 120° for 7 h but the rearranged product (**B**) was not detected and only the starting material (75%) together with the monomer alkaloid (15%) were isolated.

Instead when dimer **A** was treated [14] with HI at 145° for 7 h the complete cleavage of the N–N bond was observed giving the β-carboline monomer in good yield.

DISCUSSION

After characterization of the dimers obtained by UV irradiation of the β-carbolines was achieved, we ran some experiments to obtain information about the dimerization pathways. The analysis of the UV spectra (Cl_2CH_2) of the starting materials suggests that a π, π^* transition occurs. No change was observed when different light sources (high or low pressure Hg lamp) or different containers (Pyrex or quartz flasks) were used (Experimental).

The π, π^* nature of the initial electronically excited state was also made evident when the irradiations were performed in the presence of naphthalene[15] (8% in Cl_2CH_2); this substance quenched the photoreaction completely.

The inhibition of the photodimerization in acidic medium (HOAc or Cl_2CH_2 saturated with HCl; see the UV data in a footnote, Table 1) suggests that the nature of the photoreactive excited state is probably n, π^*; this state would originate from an intramolecular energy transfer: $(\pi, \pi^*) \rightarrow (n, \pi^*)$[16] which is inhibited under acidic conditions.

The n, π^* nature of the photoreactive state together with the radical character of the reaction (see below) suggests that this excited state is a $T_1(n, \pi^*)$ state.

The perturbation will be located at the NH group and the preferential non-emissive stabilization will be the homolytic fission of the NH bond. Hence an aminyl free radical will be formed beginning the dark radical reaction shown in Scheme 2.

In Table 1 are given UV spectroscopic data of harmane in EtOH and Cl_2CH_2 and it can be observed that these spectra are very similar. However, the reaction does not take place when EtOH is used as solvent, which might be explained taking into account two known results: (i) The H donor nature of alcohols[17] in photochemical radical reactions and (ii) the H abstracting behavior of aminyl radicals[18–21] in solvents such as alcohols, thiols, and alkylbenzenes.

Another result that supports the radical nature of this reaction is oxidation with $KMnO_4$. When β-carboline alkaloids were treated with this reagent under neutral conditions (Experimental) we obtained similar results to those described for their photolysis (Table 1) and as it is known[22–26] that $KMnO_4$ oxidation occurs by a radical mechanism. Accordingly, it was observed that photolysis is quenched when the reaction was performed in the presence of a radical trapping agent as cyclohexene (0.4% in Cl_2CH_2).

The photoreaction of β-carbolines is not affected by the presence of I_2 or O_2 (Experimental) because aryl substituted aminyls are very stable.[18]

Danen and Neugebauer[27] mentioned that a σ or a π electronic ground state is possible for the aminyl free radicals. The diphenylaminyl[27] and the 9-carbazolyl radicals[28] possess a π ground state and their characteristic delocalization of the unpaired electron into the aromatic ring was observed by ESR. The more effective delocalization in the latter is presumably due to its planar geometry.[27] Taking into account these results we can assume that the aminyl radicals formed during the UV irradiation of β-carbolines are 9-β-carbolinyl π radicals which delocalize to 3-β-carbolinyl radicals, and both N · and C · are responsible for the formation of compounds **A** and **B** (Scheme 2).

The electronic density values reported for β-carbolines[29] could explain that the delocalization only occurs, in little extension, into the pyridine ring. The absence of C–C dimers could be explained taking into account the low concentration of the 3-β-carbolinyl radicals in the solution during the irradiation.

Thus, the reaction should yield preferentially the symmetric dimer **A** and, as minor product, the asymmetric **B**.

This product distribution is modified if a steric shielding of the aminyl nitrogen atom is produced by a bulky substituent at C_1 and then the dimer **B** becomes the principal product of the reaction (harmane and harmine). In the special case of the 3, 4-dihydro-harmine the dimer **B** is not formed because the delocalization of the unpared electron into the pyridine ring to form the 3-β-carbolinyl radical is not possible.

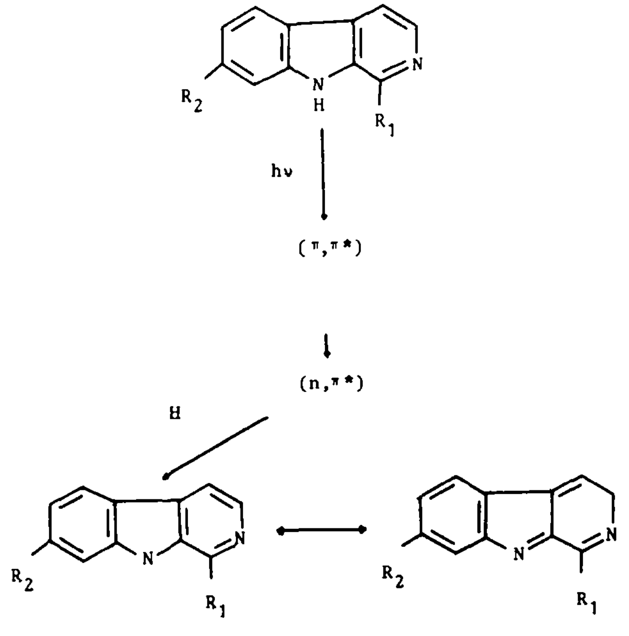
The experimental results indicated in Table 2 suggest that the stability and the lifetime of the 9-β-carbolinyl radicals are greater than those of the 3-β-carbolinyl radicals. Steric shielding of the aminyl nitrogen[30] and the mesomeric effect[31–33] are important factors contributing to the stability and long life of aminyl free radicals.

EXPERIMENTAL

Mps are uncorrected and were determined using a Kofler hot-plate apparatus. The UV and IR spectra were recorded on a Beckman DK-2A Spectrophotometer and on a Perkin–Elmer 137 spectrophotometer respectively. The ^{1}H-NMR spectra were

Table 2.

alkaloid	container	t_1(B) (min)	t_2(A+B) (min)
Harmane	Pyrex	60	150
	Quartz	15	45
Harmine	Pyrex	105	360
	Quartz	15	180



Scheme 2.

registered on a Varian A-60 spectrometer using TMS as internal standard and the MS were determined on a Varian MAT CH-7 spectrometer at 70 eV.

Compounds used for the photochemical reactions. The alkaloids harmane, harmine and harmaline employed in this work (Practical Grade reagents, Fluka AG, Buchs SG) were purified by recrystallization and characterized by m.p., UV, ^{1}H-NMR (Table 1) and MS.[9] Nor-harmane was prepared according to the method described by Harvey *et al.*,[35] its physical and spectroscopical properties are given in Table 1. 1-Ethyl-β-carboline was synthesized starting from tryptophan.[36] Colorless plates from benzene, m.p. 191–193° (lit[36] 193–195°). ^{1}H-NMR (DMSO-d$_6$) δ CH$_3$ 1.42 (3 H, t, J 8 Hz); CH$_2$ 3.22 (2 H, c, J 8 Hz); H$_6$ 7.27 (1 H, m); H$_7$ and H$_8$ 7.63 (2 H, m); H$_4$ 7.95 (1 H, d, J$_{3,4}$ 5 Hz); H$_5$ 8.23 (1 H, d, J$_{5,6}$ 6 Hz); H$_3$ 8.33 (1 H, d, J$_{3,4}$ 5 Hz); NH 11,70 (1 H, s). MS *m/z*(%): 196(M$^{+\cdot}$, 90); 195(100); 181(10); 168(45); 155(8); 141(13); 128(5); 115(10).

General method of irradiation.

The β-carboline alkaloids (25 mg) were irradiated in Cl$_2$CH$_2$ solns (50 ml) in Pyrex Erlenmeyer flasks (125 ml) with stirring. The light source was a high-pressure Hg lamp (Hanau-Quarzlampen G.m.b.H, TQ 150) which was placed 10 cm from the flasks and the irradiation time was 15 h. The progress of the reaction was followed by TLC (neutral alumina; benzene–EtOH); the spots on the plates were made visible with I$_2$ or UV light. Irradiations in EtOH were performed in a similar manner.

When the irradiation was stopped, TLC analysis showed the non-converted starting alkaloid and one or two spots in the following order (decreasing Rf values): symmetric dimer A (Scheme 1), substrate and asymmetric dimer B.

The residue obtained by evaporation of the solvent was chromatographed on a neutral aluminum oxide column. Benzene and mixtures of benzene–EtOH (0.1–2%) were used as eluents. The bands on the columns were also made visible by UV light. In all cases, the compounds eluted in the following order: first the symmetric photoproduct, second the non-converted alkaloid (identified from their Rf, m.p. and IR) and third the asymmetric photoproduct.

The conversion yields of the alkaloids and the properties of the photoproducts are indicated in Table 1.

The photoreaction of β-carboline alkaloids presented no changes when: (i) the soln was degassed with a fine stream of N$_2$ before and during the irradiation, (ii) quartz Erlenmeyer flasks were used as containers and (iii) the solns were irradiated with a low pressure Hg lamp (Hanau-Quarzlampen G.m.b.H, 5631; 0.13 A). Otherwise, no photoreaction occured when a W lamp or a W lamp and methylene blue as sensitizer were used (alkaloid 20.6 mg, sensitizer 1.5 mg, Cl$_2$CH$_2$ 50 ml) or when irradiations were performed in acidic soln (HOAc or Cl$_2$CH$_2$ saturated with HCl).

In Table 2 are indicated the time values (t$_1$ and t$_2$) at which products **A** and **B** are detected (TLC).

When the alkaloids (50 mg) were irradiated in Cl$_2$CH$_2$ solns (50 ml) to which I$_2$ (50 mg) was added, a product distribution similar to that of Table 1 was observed.

Mass spectra of β-carboline photodimers

m/z(%), compound **1**: 334 (M$^{+\cdot}$, 26) 167(100), 166(4), 140(28), 127(6), 114(8); compound **2**: 362 (M$^{+\cdot}$, 41), 181(100), 166(6), 154(64), 140(8), 127(29), 114(10); compound **3**: 362 (M$^{+\cdot}$, 100), 347(17), 335(8), 321(5), 308(5), 181(29), 166(3), 154(50), 140(2), 127(43), 114(7); compound **4**: 422(M$^{+\cdot}$, 31), 211(100), 196(10), 184(9), 180(6), 170(23), 168(24), 144(2), 141(5); compound **5**: 422(M$^{+\cdot}$, 100), 407(8), 395(5), 381(10), 368(5), 352(5), 325(7), 211(10), 196(6), 184(8), 180(7), 170(10), 168(10), 144(5), 141(5); compound **6**: 390(M$^{+\cdot}$, 22), 195(100), 194(85), 168(7), 166(18), 140(13), 127(9), 114(10); compound **7**: 390(M$^{+\cdot}$, 100), 363(4), 335(5), 332(48), 322(5), 230(9), 229(10), 224(5), 208(5), 207(5), 200(5), 195(43), 194(3), 168(15), 166(58), 140(10), 127(8), 114(11).

Oxidation of β-carboline alkaloids with KMnO$_4$

The alkaloid (20 mg) dissolved in the minimum volume of acetone, was heated at 70°. To this soln a saturated KMnO$_4$ soln (in acetone) was added dropwise.[23]

The reaction was monitored by TLC and the formation of **A** and **B** was observed. The MnO$_2$ was removed by filtration and the reaction mixture was chromatographed on a preparative TLC plate (neutral aluminum oxide; benzene–EtOH); the non-converted alkaloid and the corresponding dimers were isolated and characterized by their Rf, m.p. and MS. The results and the yields are similar to those obtained by photolysis of the same alkaloid (Table 1)

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